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COGNITIVE DEFICITS INDUCED BY ^{56}Fe RADIATION EXPOSURE

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ABSTRACT

Exposing rats to particles of high energy and charge (e.g., ^{56}Fe) disrupts neuronal systems and the behaviors mediated by them; these adverse behavioral and neuronal effects are similar to those seen in aged animals. Because cognition declines with age, and our previous study showed that radiation disrupted Morris water maze spatial learning and memory performance, the present study used an 8-arm radial maze (RAM) to further test the cognitive behavioral consequences of radiation exposure. Control rats or rats exposed to whole-body irradiation with 1.0 Gy of 1 GeV/n high-energy ^{56}Fe particles (delivered at the alternating gradient synchrotron at Brookhaven National Laboratory) were tested nine months following exposure. Radiation adversely affected RAM performance, and the changes seen parallel those of aging. Irradiated animals entered baited arms during the first 4 choices significantly less than did controls, produced their first error sooner, and also tended to make more errors as measured by re-entries into non-baited arms. These results show that irradiation with high-energy particles produces age-like decrements in cognitive behavior that may impair the ability of astronauts to perform critical tasks during long-term space travel beyond the magnetosphere.
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INTRODUCTION

Future missions in space, such as a mission to Mars, will involve long-term travel beyond the magnetic field of the Earth. As a result, astronauts will be exposed to radiation qualities and doses that differ from those experienced in low earth orbit, including exposure to heavy particles, which are a component of cosmic rays. High-energy particles (HZE particles), such as silver or iron particles of high energy and charge, have been shown to exert very potent damaging effects on cells (Todd, 1983; Todd et al., 1985), and much lower doses of these particles are likely to produce damage similar to that of higher doses of other types of radiation.

For several years, research from our laboratories has been directed toward the determination of the behavioral and neuronal effects following exposure to these types of radiation in animals. In these previous experiments (Joseph et al., 1992; Joseph et al., 1993; Joseph et al., 1998; Joseph et al., 2000; Rabin et al., 1994; Rabin et al., 1998; Rabin et al., 2000; Shukitt-Hale et al., 2000) we have shown that whole-body exposure of rats to HZE particles, primarily 600 MeV or 1 GeV ^{56}Fe, can produce deficits in behavior and neurochemistry, even at relatively low doses (0.1 Gy). Exposing rats to HZE particles disrupts the functioning of the dopaminergic system and behaviors mediated by this system, such as motor performance and amphetamine-induced conditioned taste aversion learning (Joseph et al., 1998; Rabin et al., 1998; Rabin et al., 2000). The effects of HZE particles, like those of other types of radiation, at both cellular and behavioral levels, have been compared to those produced by aging (Joseph et al., 1992; Joseph et al., 1993; Joseph et al., 1998; Joseph et al., 2000; Shukitt-Hale et al., 2000).

Our results show that exposing rats to ^{56}Fe particles disrupts behaviors mediated by the dopaminergic system and produces changes in these endpoints similar to those seen in old animals. Cognitive function has been shown to deteriorate profoundly in aging, which may be related to an increase in the release of reactive oxygen species (ROS) seen during aging (Ames et al., 1993; Harman, 1992; Shukitt-Hale, 1999). Because irradiation causes a similar increase

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in ROS (Joseph, 1992; Joseph et al., 1998), we hypothesized that exposure to heavy particles would also affect cognitive performance, particularly spatial learning and memory, which is highly impaired in aging.

In aged animals, memory alterations appear to occur primarily in secondary memory systems and are reflected in the storage of newly acquired information (Bartus et al., 1982; Joseph, 1992). Aged animals show decrements in spatial memory pe mance, i.e., the ability to acquire a cognitive representation of location in space and the ability to effectively navigate the environment (for reviews see Barnes, 1988; Brandeis et al., 1989; Gallagher and Pelleymounter, 1988; Ingram et al., 1994). Several paradigms have been used to test spatial learning and memory in aged animals, primarily the Morris water maze (MWM) and the radial arm maze (RAM). The performance of aged rats is impaired in these tests, and the poorer performance is considered to reflect a deficit in the ability of the organism to utilize spatial information (Brandeis et al., 1989; Gage et al., 1984; Gallagher and Pelleymounter, 1988; Ingram et al., 1994; Kobayashi et al., 1988; Rapp et al., 1987; Shukitt-Hale et al., 1998; Wallace et al., 1980).

Therefore, given our previous research and age-radiation parallels, we have established a program to determine the effect of exposure to ^{56}Fe particles on cognitive behaviors known to deteriorate with aging. In our initial study, we assessed spatial learning and memory in 4 month old Sprague-Dawley rats in the Morris water maze one month following whole-body irradiation with 1.5 Gy of 1 GeV/n high-energy ^{56}Fe particles (Shukitt-Hale et al., 2000). Irradiated rats demonstrated cognitive impairment compared to the control group as evidenced by increased latencies to find the hidden platform, particularly on the probe trials (swim with no platform) and on the reversal day when the platform was moved to the opposite quadrant and the rats had to learn a new platform location (and forget the old location). The irradiated rats did not use spatial strategies during the probe trials, reflecting a deficit in the ability to utilize spatial information. These findings are similar to those seen in aged rats, suggesting that an increased release of ROS may be responsible for the induction of radiation- and age-related cognitive deficits.

To characterize further the cognitive deficits seen during radiation, the present study used the RAM test to measure spatial and short-term memory changes in control animals or animals that received 1.0 Gy of ^{56}Fe radiation. Different mazes have been found to tap a variety of processes that contribute to, or affect, spatial learning (Hodges, 1996), and the RAM is appropriate for detecting reference and working memory deficits in the same apparatus. Furthermore, as stated above, the RAM paradigm has previously been shown to be sensitive to age-related changes (Gallagher and Pelleymounter, 1988; Kobayashi et al., 1988; Wallace et al., 1980).

METHODS

Animals

Fourteen male Sprague-Dawley rats (Taconic Farms, Germantown, NY), 8 radiated and 6 control, were used in this study. The animals were 3 months of age when exposed to radiation at Brookhaven National Laboratory (BNL) in Upton, NY. One week following radiation, all rats were shipped to the USDA, Human Nutrition Research Center on Aging at Tufts University (HNRCA) in Boston, MA, where they were allowed to acclimate before testing at 12 months of age (9 months following irradiation). At the HNRCA, the rats were individually housed in hanging wire mesh cages with *ad libitum* access to food and water in a colony maintained at constant temperature (21°C+/- 1°), on a 12-hour light/dark cycle.

Dosimetry and Irradiation Procedures

Radiated rats were exposed to 1.0 Gy whole-body irradiation with high-energy ^{56}Fe particles (1 GeV/n) at the AGS (Alternating Gradient Synchrotron) at BNL at a dose rate of approximately 1 Gy/min. The rats were irradiated one at a time in well-ventilated plastic holders that minimized movement. Non-irradiated rats were taken to the BNL beam facility, but because of beam time considerations were not placed in the beam line apparatus in the exposure cave.

Energy from radiation with 1 GeV/n ^{56}Fe provided a Bragg curve with the plateau region extending 8 cm in water. Since the diameter of the rat (including the plastic restrainer) was 7 cm, the animals were within this plateau region of the curve. Using X-ray film to visualize the position of the rat restrainer relative to the beam, the rats were positioned so that their heads were located in the center of the beam. Because the beam diameter was ≈ 7 cm, some portion of the upper torso of the rats was also irradiated. A full description of the dosimetry methods and characterization of the 1 GeV/n beam at the AGS has been published recently (Zeitlin et al., 1998).

Radial Arm Maze

The 8-arm RAM was used to assess spatial learning and memory (Olton, 1987). In the RAM, a win-shift strategy is optimal since the rat must retrieve the reward at the end of each baited arm without entering unbaited arms and without returning to any previously visited arm, because visited arms are not rebaited. This test requires the rat to use visual cues as well as working memory to monitor which arms have been visited when selecting which arm to visit next.

The Plexiglas RAM consisted of eight equally spaced arms (70 cm long, 12 cm wide, and 15 cm high) radiating

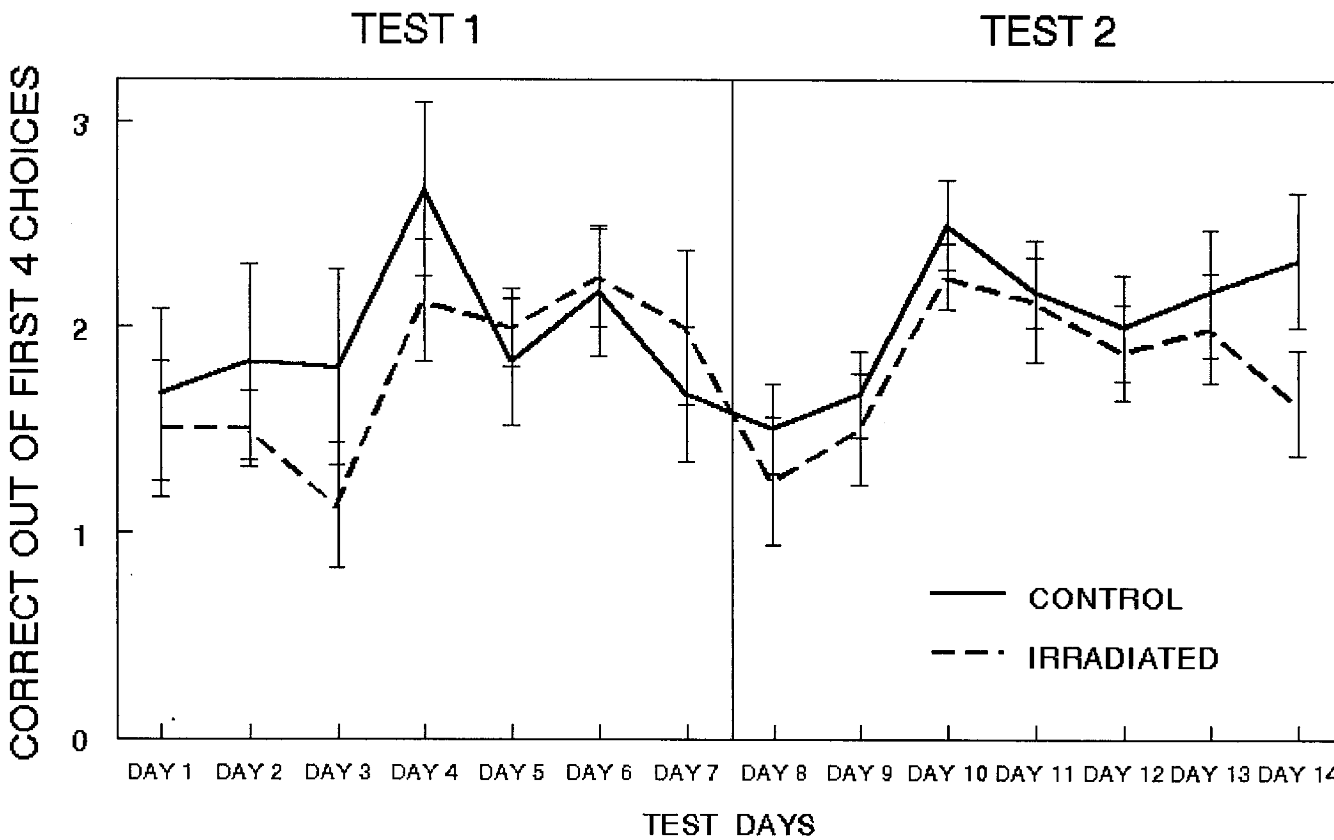

Fig. 1. Effects of 1.0 Gy of ^{56}Fe radiation on the number of correct entries out of the first four choices made by control or irradiated animals in the RAM task (mean ±SEM). The task was divided into two 7-day test sessions with different maze configurations. Day 1 represents the first day of Test 1 and Day 8 represents the first day of Test 2.

from an octagonal central arm 30 cm in diameter. A Plexiglas ring surrounded the central area, preventing the rat from entering any of the arms. An overhead pully and rope enabled the experimenter to raise the ring and allow the rat to leave the central area and select from any of the eight arms. Each maze arm contained a small dish at its end which could be baited with 0.25 ml of 0.30% saccharin solution. The maze was surrounded by a white curtain and a different randomly placed visual cue was attached to the end of each arm.

All rats were placed on a water-restriction schedule 5 days prior to behavioral testing which consisted of access to fluid for one hour per day. Subjects had daily access to water (1 hour/day) one hour after the end of each experimental session. The animals were also gradually introduced to saccharin solution (0.30%) in order to avoid taste aversion to a novel substance during RAM testing. After 2 days of habituation to the RAM, the subjects began testing. The experimental procedure consisted of 14 single trials (1 per day), split into two test sessions. For test 1, consisting of 7 trials, saccharin solution placed in a small dish at the end of four pre-selected arms (at 45°, 90°, 180°, and 315°). A different randomly placed visual cue was attached to the end of each arm. The session began when the rat was positioned in the center of the maze for 15 seconds and was then freely permitted free access to all 8 arms. The test was terminated when: a) the animal made 12 full entries (a full entry was considered to be all four paws of the rat

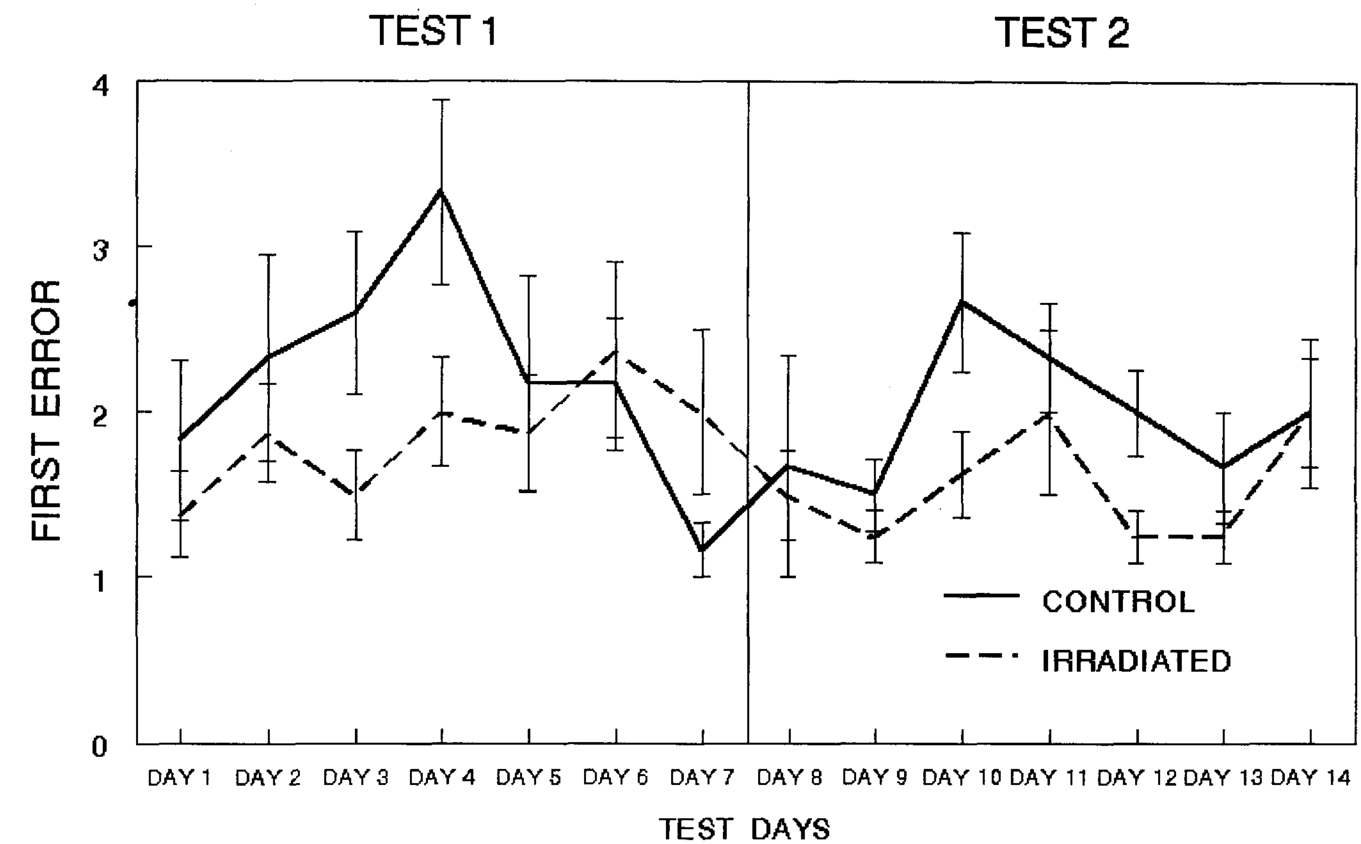

Fig. 2. Effects of 1.0 Gy of ^{56}Fe radiation on the rank of occurrence of the first error (out of four choices) made by control or irradiated rats in the RAM task (mean ±SEM). The task was divided into two 7-day test sessions with different maze configurations. Day 1 represents the first day of Test 1 and Day 8 represents the first day of Test 2.

inside the arm), b) the animal entered the 4 baited arms, or c) 10 minutes elapsed, whichever came first. The 7 trials of test 2 were procedurally identical to test 1. However, for this portion of the study, the visual cues at the end of the maze arms were exchanged for new cues and the bait was placed in 4 arms (45°, 90°, 135°, and 225°) different from those baited during the first 7 days of testing. Cues and baited arms were changed to examine how fast the subject could relearn new spatial cue-maze arm associations.

The following dependent measures were recorded by experimenter observation: the order of entry into the maze arms; the total number of correct entries; the total number of errors, broken into non-baited arm entries and revisits to both non-baited and baited arms; the choice on which the first error was made; the total numbers of choices; the time to complete a session; and the number of correct entries out of the first four choices. In addition, time per choice was calculated as total time for completion of the session divided by total number of entries.

RESULTS

Exposure to 1.0 Gy of ^{56}Fe radiation adversely affected RAM performance, although the effects were more subtle than those seen in aged animals. Even though most of the parameters measured did not seem to be significantly modified by exposure to HZEs, there appeared to be a trend in the measured behaviors that parallel those of aging.

As seen in Figure 1, analysis of variance (ANOVA) indicated that irradiated animals made significantly fewer correct choices out of the first 4 choices than did controls ($F(1,12) = 5.42$, $p<0.05$) over the course of the 14 days of testing, i.e., irradiated rats made more errors on the first 4 choices by entering either non-baited arms or revisiting arms. In addition, irradiated animals tended to produce their first error sooner than control rats (Figure 2) ($F(1,12) = 3.19$, $p=0.09$) and also tended to reenter non-baited arms more often (Figure 3) ($F(1,12) = 3.20$, $p=0.09$).

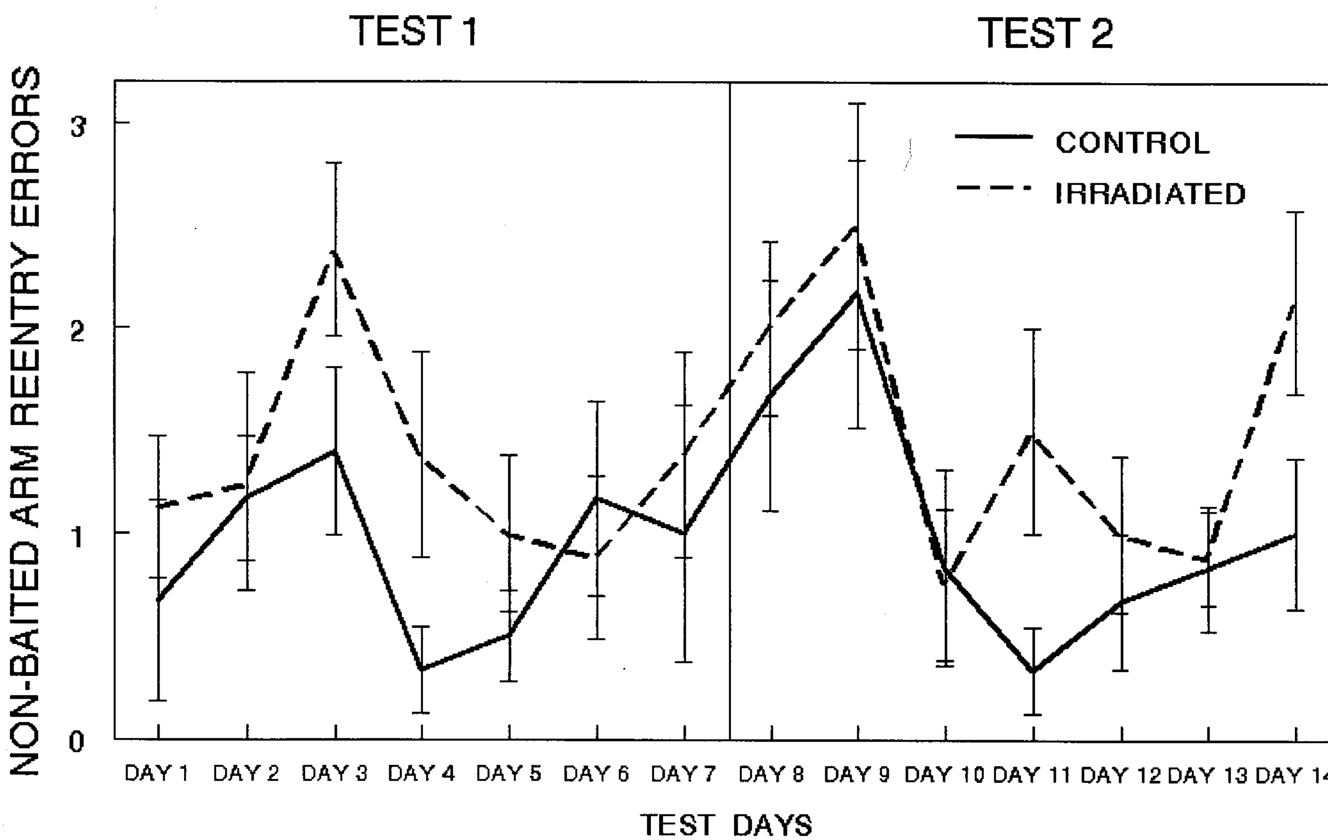

Fig. 3. Effects of 1.0 Gy of ^{56}Fe radiation on the number of non-baited arm reentries made by each day by control or irradiated rats in the RAM task (mean ±SEM). The task was divided into two 7-day test sessions with different maze configurations. Day 1 represents the first day of Test 1 and Day 8 represents the first day of Test 2.

ANOVA also revealed a significant effect of test session on most of the measured behaviors, i.e., that performance on the two tests was dissimilar, including: non-baited arm entry errors, $p<0.05$; total test time, $p<0.01$; total errors, $p<0.05$; time/choice, $p<0.05$; and total correct, $p<0.05$. Non-baited arm entry errors, total errors, and total correct were higher in test 2 compared to test 1, while time/choice and total test time were lower in test 2.

ANOVA also demonstrated a significant day effect on several parameters, for the most part showing that the rats learned the task over time: correct out of 4, $p<0.01$; first error, $p<0.05$; non-baited arm reentry errors, $p<0.05$; total test time, $p<0.01$; total errors, $p<0.05$; and total correct, $p<0.05$.

DISCUSSION

In the this experiment we hypothesized that the animals irradiated with 1.0 Gy of ^{56}Fe radiation would show similar deficits in RAM performance as those of aged rats (Gallagher and Pelleymounter, 1988; Kobayashi et al., 1988; Wallace et al., 1980). Even though some of the effects on RAM performance that we found in irradiated animals parallel those of aging, for the most part they were subtle. The parameters that were affected in the irradiated rats, i.e., more errors on the first 4 choices, reentering non-baited arms more often, and production of the first error sooner than control rats, tended to be measures dependent on both reference and working memory, rather than speed. The results of the present study are similar to those reported previously regarding the effects of radiation as most of the studies showed some degree of decline produced by exposure to ^{56}Fe radiation. X-ray irradiation has also been shown to impair the ability to use distal visuospatial cues, however much higher doses (20-25 Gy) are needed to produced this effect (Hodges et al., 1998).

Research investigating the effects of aging on RAM performance has demonstrated that aged animals, when navigating the maze so as to obtain a reward, enter baited arms with less frequency and re-enter both baited and non-baited arms more often than do younger animals, (i.e., commit more errors) (Amassari-Teule and Marsanich, 1996; Brandeis et al., 1990), have less initial correct responses (Kobayashi et al., 1988; Wallace et al., 1980), and make their first error sooner than younger animals (Kobayashi et al., 1988). This pattern of behavior illustrates a generalized inability of older rats to remember where the bait was previously placed in the maze, thus indicating a possible age-related decline in spatial memory and their flexibility to reset their mental images. The irradiated animals in our study showed a similar decline in these parameters. Specifically, irradiated subjects entered the rewarded arms within the first 4 trials significantly less often than did the non-radiated animals. In addition, irradiated animals made more errors in that they re-entered non-baited arms more often and entered an incorrect arm sooner than did controls. It must be mentioned, however, that the latter findings did not quite reach statistical significance, possibly due to the large variability found between subjects, or the small number of subjects in the study.

Contrary to the results found by prior research investigating the effects of aging on RAM performance (Ammassari-Teule et al., 1994; Amassari-Teule and Marsanich, 1996; Brandeis et al., 1990; Tanila et al., 1997), the subjects in this study did not differ in the amount of time spent solving this task. Old animals generally take longer to solve the radial maze task (Ammassari-Teule et al., 1994), which was not the case with the irradiated animals. In fact, time taken to complete the test and time per choice decreased in both groups from test 1 to test 2. This result is similar to that found in another radiation study where running time in a maze was not significantly affected by gamma radiation, whereas errors were, most notably when subjects were challenged or required to "reorganize" a pre-irradiation response pattern into a new pattern (Urmer and Brown, 1960).

The decrease in spatial memory with exposure to 1.0 Gy of ^{56}Fe radiation in this study is similar to what we found in our previous study, where we showed that whole-body irradiation with 1.5 Gy of ^{56}Fe radiation disrupted spatial learning and memory, as assessed by the Morris water maze, one month following exposure in 4 month old animals (Shukitt-Hale et al., 2000). We found that the irradiated rats were not using spatial strategies to solve the maze (Shukitt-Hale et al., 2000), which also appears to be the case in the present study, although the effects are more subtle in this study, which could be due to a number of reasons. First, the dose used in this study was lower than that used in our previous study (1.0 Gy vs. 1.5 Gy). It could be that the threshold for the radiation effect on spatial memory is close to 1.0 Gy when using iron particles. The second reason is that the rats in this study were tested 9 months following irradiation, rather than 1 month in the previous study; the effectiveness of the radiation could be directly related to time following exposure, with longer times being less effective. Another explanation for the more subtle effect in the present study is the fact that the rats were older than in the previous study (12 months vs. 4 months); at 12 months of age, rats already show decrements in spatial learning and memory performance (Shukitt-Hale et al., 1998). Therefore, control rats could already be showing performance decrements so that it makes it harder to detect an effect of radiation. Furthermore, another possibility is that the paradigm used in this study was too difficult for the subjects to solve. It is possible that by changing the cues and the configuration of the baited arms at the beginning of test 2, as well as by having too many spatial cues (one per arm), the test was rendered too hard to solve. This difficulty may have confused the animals enough to mask the true effects produced by ionizing radiation.

There are several findings that lends credence to some of these hypotheses. Both irradiated and control subjects spent an unusually long time solving this task when compared to other studies. Other studies using the RAM paradigm have documented that control animals, once trained, take about 1 to 3 minutes to solve this task. For example, Kadar and colleagues (1989) found that while young animals (3 months) finished the task in around 2 minutes, 12-month old animals spent an 3 additional minutes to solve the same paradigm. Our subjects, on average, never performed faster than 6 minutes. It would also be expected that test time would initially increase at the start of test 2 as the animals re-learned a new set of spatial cues and a different configuration of baited arms; however this did not occur in either group, possibly showing that the animals never really learned the initial task. Therefore, it could be that the animals were too old and that our task was too difficult for the animals to perform, and that training the rats in the RAM first (i.e., baiting all eight arms and then only baiting four arms) would have enabled us to see differences between the groups. A study in progress now in our laboratory is exploring these questions as we are testing a 4 month old group of rats, 1 month following radiation, in the RAM, and training them with all eight arms baited first and with cues around the maze, not at the ends of the arms.

Our program has shown adverse effects of high-energy iron particles on a variety of behavioral tasks, including cognitive tasks which require spatial learning and memory, similar to those seen in aging (Shukitt-Hale et al., 2000). Based on these findings, and given that both radiation exposure and the aging process may involve oxidative stress (Harman, 1954; Sun et al., 1998), it may be reasonable to assume that these shared behavioral effects may be produced by the same mechanism, i.e., oxidative stress damage to the central nervous system caused by an increased release of reactive oxygen species. The high behavioral toxicity of low doses of HZE particles suggests that these decrements in behavior may impair the ability of astronauts to perform critical tasks during long-term space travel beyond the magnetosphere. Future research should focus on a more thorough evaluation of the behavioral and neurochemical effects of HZE particles, the mechanisms by which HZE particles affect behavior, and possible nutritional modification procedures (e.g., antioxidants, phytochemicals) to offset the deleterious effects of heavy particles in space.

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